Multimorbidity in Anti-Neutrophil Cytoplasmic Antibody-associated vasculitis

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ABSTRACT

Objectives

ANCA-associated vasculitis (AAV) is considered a chronic, relapsing condition. To date, no studies have investigated multimorbidity in AAV nationally. Here, we characterise temporal trends in multimorbidity and report excess healthcare expenditure associated with it in a national AAV cohort.

Methods

AAV patients diagnosed between 1997 and 2017 were matched with five general population controls. Linked morbidity and healthcare expenditure data were retrieved from a national hospitalisation repository and nationally-published cost data. Multimorbidity was defined as the development of ≥2 disorders. Pre-specified morbidities were analysed individually and together over time using modified Poisson regression, discrete interval analysis and Chi-squared test for trend. The relationship with healthcare expenditure was investigated using multivariate linear regression.

Results

543 AAV patients (58.7 [48.9-68.0] years; 53.6% male) and 2,672 controls (58.7 [48.9-68.0] years; 53.7% male) were matched and followed-up for 5.1 years. AAV patients were more likely to develop individual morbidities at all timepoints, but especially <2 years post-diagnosis. The highest proportional risk was observed for osteoporosis (adjusted incident rate ratio 8.0, 95% CI 4.5-14.2). After one year, 23.0% of AAV patients and 9.3% of controls were multimorbid ($p<0.0001$). After ten years, 37.0% of AAV patients and 17.3% of controls were multimorbid ($p<0.0001$). Multimorbidity was associated with disproportionate increases in healthcare expenditure in AAV patients. Healthcare expenditure was highest for AAV patients with ≥3 morbidities (3.89, 95% CI 2.83-5.31; $p <0.001$ *versus* no morbidities).

Conclusions

Our findings emphasise the importance of holistic care in AAV and identify a potentially critical opportunity to consider early screening.

INTRODUCTION

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a set of systemic autoimmune diseases, comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[1] With modern immunosuppressive therapy, these previously fatal diseases have become chronic, relapsing conditions with mean five-year survival rates of ~70%.[2]

With improved survival, AAV patients are now at an increased risk of multimorbidity, defined as the presence of two or more concurrent long-term disorders.[3] Multimorbidity is increasingly common in the general population[4] and has also been described in other chronic inflammatory conditions including rheumatoid arthritis.[5,6] It complicates chronic disease management and is associated with reduced functional status, decreased quality of life and increased mortality.[7,8] Multimorbidity also has important implications for the organisation and delivery of healthcare, which is traditionally structured to optimise the management of individual diseases.[9]

Previous studies have demonstrated an increased risk of several individual morbidities in AAV, including cardiovascular disease, diabetes mellitus and venous thromboembolic disease.[10-13] These associations are thought to be a consequence of chronic inflammation or the increasingly potent and toxic medications used to treat AAV.[14] However, to our knowledge, no studies have yet investigated the frequency or burden of multimorbidity in AAV patients. In this national multi-centre data-linkage study, we compare temporal trends in the incidence of a wide range of individual morbidities and multimorbidity between AAV patients and matched general population controls, and report the cost of excess resource consumption attributable to multimorbidity in AAV patients.

METHODS

Study design and data linkage

We performed a retrospective, matched-cohort population-based data-linkage study using routine healthcare data from multiple national registries (**Supplementary Figure 1**). Record linkage was conducted by NHS Scotland using a robust methodology that has previously been shown to produce highly accurate and complete data.[15,16]

Study population

AAV patients were identified by clinicians using the European Medicines Agency criteria[17] in seven secondary and tertiary care hospitals across Scotland. Patients were eligible for inclusion if they were diagnosed with AAV after 1st January, 1995 and were aged 16 years or older at the time of data-linkage. The date of AAV diagnosis was assigned as the index date. Each patient was matched with at least one, but up to five, general population controls based on age (±2 years), sex and postal ('zip') code of residence. General population controls were assigned the same index date as their matched AAV patient.

Study follow-up

Patients were followed-up from the index date until their date of death or 28th February 2017, whichever came first. Information regarding cause of death was obtained via data linkage from the National Records of Scotland death registry, which records all deaths in Scotland.[18]

Definition and identification of individual morbidities and multimorbidity

Morbidities were defined as clinically distinct diseases co-occurring with AAV, but which were not a direct complication of AAV itself (e.g. chronic kidney disease, neuropathy, arthritis and sino-nasal disease). Our analysis focused *a priori* on a set of twelve individual morbidities of public health concern in elderly populations, which were identified following discussions between senior co-authors and an extensive review of the relevant multimorbidity literature (**Supplementary Figure 1**).[19,20] The majority of these morbidities have previously been shown to be identifiable from administrative datasets with moderate to high validity.[20] Multimorbidity was defined as the presence of two or

more disorders and was determined by summing each patient's individual morbidities at specific timepoints (years 1, 2, 5 and 10). Information regarding each patient's morbidities was obtained via data linkage with a national, population-based hospitalisation repository. This registry holds information on the discharge codes of all Scottish hospitalisations since the 1980s and details up to five diagnoses per admission.[21] The first diagnosis corresponds to the primary reason for hospitalisation, whilst the remaining diagnoses capture information regarding the patient's morbidities. All diagnostic codes recorded for each hospitalisation were included in this analysis.

Morbidities were identified using previously validated International Classification of Diseases (ICD) codes (ICD-9 pre-1996; ICD-10 post-1996) and are listed in **Supplementary Table 1**.[20,22,23] The first date that a relevant diagnostic code appeared in a patient's record was assigned as the incident date for that specific morbidity. Individual morbidities identified during the five years prior to the patient's enrolment in the study (i.e. prior to the index date) were classified as pre-existing morbidities and were thus excluded from the analysis. This duration of 'look-back' period has previously been shown to allow the accurate determination of incident from prevalent morbidities when using routine healthcare data.[24]

Determination of healthcare expenditure

Count data regarding the number of outpatient encounters, inpatient hospitalisations and overall length of inpatient stay (on both general medical wards and intensive care units) were obtained via data-linkage with the Scottish outpatients and hospitalisations registries for each study year (**Supplementary Figure 1**). The NHS Scottish Health Service Costs Book was used to obtain annual tariffs for resource consumption.[25] Tariffs were inflated to 2016 values using the Hospital and Community Health Service (HCHS) Index. Inaccessible data regarding tariffs from pre-2002 were estimated using the 2002 tariff as the reference for deflation.

Statistical analysis

Baseline characteristics were summarised for AAV patients and matched general population controls. Incident morbidities were summed for each participant and used to

derive an ordinal variable representing patients with 0, 1, 2, or 3 or more morbidities. Differences in the proportions of AAV patients and general population controls in each of these categories were compared using the Chi-squared test for trend.

The overall risk for individual morbidities in AAV and controls were compared using modified Poisson regression models, adjusted for age, sex, and local health board.[26,27] Discrete-time analysis was conducted with follow-up at 1, 2, 5 and 10 years using Lexis expansions.[28] These timepoints were selected *a priori* based on current treatment guidelines on the duration of induction and remission therapy in AAV,[29] in order to provide sufficient granularity to observe potential temporal changes in the occurrence of morbidities. The incidence rates for individual morbidities at each interval was calculated by dividing the number of morbidities observed in each interval by person-years of follow-up included in each interval. Ninety-five percent confidence intervals (95% CIs) were computed using the Poisson assumption.[30]

A multivariate linear regression model, adjusted for age, sex and deprivation status (**Appendix**), was created to determine the relationship between number of individual morbidities and healthcare expenditure. As the residuals were not normally distributed, the continuous dependent variable 'healthcare expenditure' was log-transformed using the natural logarithm. Homoscedasticity was evaluated using the Breusch-Pagan test. All analyses were performed in Stata (version 14)[31] and R (version 3.6.1).[32]

Ethical considerations

This study was conducted in compliance with the Helsinki Declaration. Approval was received from the Scotland Research Ethics Committee A (Reference: 15-SS-0152). Individual patient consent was not required as the research was approved by the Public Benefit and Privacy Panel for Health and Social Care who oversee studies accessing anonymised healthcare data held by the NHS Scotland. Information governance, confidentiality and data protection were undertaken according to the Data Protection Act (1998). All study data were analyzed and held within a unique, secure national safe haven environment[33] administered by the Electronic Data and Innovation Service (eDRIS), NHS Scotland.

RESULTS

Five-hundred and forty-three AAV patients (median age at index 58.7 [48.9 to 68.0] years; 53.6% male) were matched with 2,672 general population controls (median age at index 58.7 [48.9 to 68.0] years; 53.7% male) and followed-up for a median of 5.1 [2.5 to 9.4] years (**Table 1**). Three hundred and sixteen (58.2%) AAV patients had GPA, 157 (28.9%) had MPA, and 68 (12.5%) had EGPA. PR3-ANCA was present in 52.7% (286/543) AAV patients and MPO-ANCA was present in 34.6% (188/543) AAV patients. A total of 12.0% (65/543) AAV patients were classified as ANCA negative.

Risk of developing individual morbidities in AAV

The risk of developing most individual morbidities was higher in AAV patients than in general population controls (**Figure 1**). The morbidity most frequently observed in AAV patients during study follow-up was hypertension (19.7% [92/466] in AAV patients *versus* 9.4% [234/2,482] in general population controls; p<0.0001) (**Table 2**). However, the highest proportional risk difference between AAV patients and general population controls was observed for osteoporosis (adjusted incident rate ratio [IRR] 8.0, 95% CI 4.5 - 14.2) (**Figure 1**). A sensitivity analysis exploring the proportional risk of hospital admissions due to hip fractures was performed to validate this finding. The risk of hip fractures in AAV patients was found to be twice that of general population controls (adjusted IRR 2.0, 95% CI 1.1 - 3.7). To explore the influence of surveillance bias, a further sensitivity analysis was performed to evaluate the proportional risk of hypothyroidism and stroke in only those patients and controls with a record of at least one hospitalisation during study follow-up (**Supplementary Results**).

Temporal trends in individual morbidities and multimorbidity in AAV

Figure 2 illustrates trends in the incidence of individual morbidities over time following AAV diagnosis. In general, the highest incidence for most morbidities was observed during the first two years of follow-up. This was especially marked for hypertension and hypothyroidism. However, a further increase in the incidence of several morbidities, including cardiovascular disease, diabetes mellitus and chronic pulmonary disease, was also noted from five to ten years after AAV diagnosis.

The proportion of study participants developing at least one incident morbidity increased over time in both AAV patients and general population controls (**Figure 3**). However, at every timepoint, AAV patients developed a significantly higher number of individual morbidities than general population controls (**Figure 3**; $p<0.0001$ for all timepoints). Multimorbidity (defined as the presence of two or more disorders) was also more common in AAV patients than general population controls at all timepoints. For example, after one year of follow-up, 23.0% (125/543) of AAV patients could be considered multimorbid *versus* 9.3% (248/2,672) of general population controls ($p<0.0001$). Ten years after diagnosis, a further 37.0% (101/273) of AAV patients had developed multimorbidity, compared with 17.3% (235/1,362) of general population controls ($p<0.0001$).

Healthcare expenditure attributable to multimorbidity in AAV patients

Figure 4 illustrates the relationship between number of individual incident morbidities and the total cost of excess resource consumption due to outpatient encounters and inpatient hospitalisations (to both general medical wards and intensive care units) in 502 AAV patients during study follow-up. Multivariate linear regression modelling confirmed that the development of multimorbidity was associated with a proportionally higher cost of excess resource consumption in AAV patients (**Supplementary Table 2**). Compared to the development of no morbidities during study follow-up, the development of two morbidities was associated with a 2.78-fold (95% CI 2.09 - 3.71; $p<0.0001$) increase in healthcare expenditure in AAV patients, whilst the development of three or more morbidities was associated with a 3.89-fold (95% CI 2.83 - 5.31; $p<0.001$) increase in healthcare expenditure in AAV patients. The increases in total healthcare expenditure observed with the development of multimorbidity are predominantly related to increases in inpatient, rather than outpatient, healthcare expenditure (**Supplementary Results; Supplementary Tables 3 and 4**).

DISCUSSION

This is the first study to describe longitudinal trends in the incidence of multimorbidity and report the healthcare expenditure attributable to multimorbidity in a large, national cohort of AAV patients. We report a number of important observations. First, AAV patients are at a significant risk of developing individual morbidities throughout their disease course, but especially in the first two years following diagnosis. Second, multimorbidity (the presence of two or more disorders) is common in AAV patients and increases significantly in frequency over time. Indeed, it affected almost one-quarter of AAV patients in their first year after diagnosis, but over one-third by year ten of follow-up. Third, multimorbidity is associated with an approximately three-fold increase in excess healthcare expenditure in AAV patients.

Uniquely, our study demonstrates that AAV patients are at an increased risk of developing multimorbidity compared to general population controls. Whilst the impact of multimorbidity has not been studied previously in AAV, we also found that multimorbidity is associated with a disproportionate increase in the cost of overall excess resource consumption. In comparison to AAV patients with no morbidities, the development of multimorbidity in AAV patients is associated with a two- to four-fold increase in total healthcare expenditure, but a three- to five-fold increase in inpatient healthcare expenditure. Relevant studies in other chronic disease populations, for example in patients with cardiovascular[34] or chronic kidney disease[35] have also demonstrated that multimorbidity is becoming the rule rather than the exception.[9,36] The implications of this are significant, given the striking association of multimorbidity with polypharmacy, greater resource consumption, reduced quality of life and poorer outcomes.[7-9,37]

Our findings are also consistent with previous assessments of individual morbidities in AAV. In relation to the risk of cardiovascular disease, we demonstrate an increased risk in both early and late stages of AAV.[10,11,38] Uniquely, our study extends these findings to other cardiovascular disorders including valvular disease and arrhythmias, both of which demonstrate a similar bimodal risk pattern over time. Although primary cardiovascular disease is relatively uncommon in AAV, the observed risk may be due to a combination of chronic inflammation and corticosteroid toxicity.[39,40] It is possible that these findings

are partly explained by surveillance bias. For example, valvular heart disease may have been diagnosed during routine echocardiography, which AAV patients are more likely to undergo than general population controls.

As general population controls were not selected from the timepoint of a new diagnosis, the increased risk observed for several morbidities early in the AAV disease course may also be explained by surveillance bias due to the additional investigations performed in AAV patients following their index diagnosis. For example, AAV patients are commonly tested for hypothyroidism as part of their diagnostic work-up. Nevertheless, an increased risk of hypothyroidism has previously been demonstrated in AAV patients prior to diagnosis, which aligns with accumulating evidence supporting shared mechanisms across the autoimmune disease spectrum.[41] Similarly, the increased risk of osteoporosis in AAV patients observed in the present study may be related to current guideline recommendations for dual energy x-ray absorptiometry (DEXA) scans when patients commence corticosteroids.[29] Hip fractures are a reliable surrogate end-point unlikely to be affected by surveillance bias and as a result we performed a sensitivity analysis to evaluate the risk of hip fractures during follow-up. Interestingly, we observed that the risk of hip fractures in AAV patients was twice that of general population controls - verifying our finding that osteoporosis risk is indeed increased in AAV patients.

Our findings have important implications for clinical practice. Specifically, the results of our temporal analysis highlight the importance of early screening for many common conditions in AAV patients, whilst also highlighting the significance of late-onset cardiovascular disease and diabetes mellitus. Our observation that peptic ulcer disease is no more likely in AAV patients than general population controls, despite the administration of high-dose corticosteroids to the former group, also appears to reflect the relative success of prophylactic therapies aimed at suppressing gastric acid secretion. Therefore, our data encourage similar preventative strategies for other morbidities.

Further research is required to understand what exact mechanisms underlie the increased risk of multimorbidity we observed in AAV patients. Given the relationship between multimorbidity and adverse pharmacological effects, such work could ultimately

incentivise a shift towards a reduction in the use of pharmacological therapies associated with numerous adverse effects, such as corticosteroids. Indeed, with the transformation of AAV into a chronic disease, it is timely to prioritise a more holistic approach towards the management of AAV patients. This is analogous to the concept of 'cancer survivorship', which has been established in oncology in response to improvements in cancer-related mortality. The overarching aim of cancer survivorship is to address the physical, psychological and social health burden that arises as a consequence of cancer patients living for longer.[42] Clinicians must therefore consider how best to organise and deliver healthcare to AAV patients, in order to fully address both their multimorbidity and their primary disease. Greater collaboration with primary care providers is likely be critical to the potential success of any such move towards a more holistic approach to patient care in AAV.

Our study has several important strengths. Utilising one of the largest cohorts of AAV patients, we adopted a comprehensive approach for improving our understanding of the burden associated with multimorbidity in AAV patients. Indeed, our method for identifying AAV patients suitable for inclusion in our cohort was also robust. We also assessed prevalent morbidity burden using a validated length of 'look-back' period[24] and previously-verified ICD discharge coding,[20,22,23] which has a reported accuracy of ~96% for common diagnoses recorded in SMR01.[43]

However, a number of limitations must be considered. First, our study identified morbidities from secondary care records, which mostly capture major disorders. Despite including all available diagnostic codes, relatively minor disorders may have been overlooked by secondary care coders and so our incidence estimates are likely to be conservative. However, this will have affected AAV patients and general population controls equally. Second, given the higher hospitalisation rate observed in AAV patients (98% *versus* 79%), the incidence rate ratios for conditions managed in primary care are likely to be over-estimates. To address this limitation, we performed a sensitivity analysis including only those patients and controls with a hospitalisation record and found that the degree of over-estimate was small for hypothyroidism, stroke and myocardial infarction (see **Appendix**). Third, patients not hospitalized in the five years prior to their index date

were classified as having no pre-existing morbidities. It is therefore difficult to be certain exactly when these patients developed 'incident' morbidities. To limit the impact of this, we employed a validated[24] fixed five year look-back period to standardize the identification of baseline morbidities across all patients. Fourth, study follow-up was limited to a median of five years, which may partly explain why we failed to demonstrate an increased risk of depression or dementia in AAV patients. Although sufficient for identifying relatively acute-onset conditions, longer follow-up is required to reliably establish the occurrence of more gradual-onset disorders, such as depression and dementia. Fifth, despite being one of the largest studies of its kind, we were unable to undertake stratified analysis by AAV type due to a lack of statistical power.

In conclusion, this novel study is the most comprehensive and detailed analysis of multimorbidity in AAV patients to date. AAV patients are at a high risk of individual morbidities, especially early in their disease course. Multimorbidity is also common in AAV patients and is associated with disproportionate increases in healthcare expenditure. Our findings emphasise the importance of holistic care in AAV patients and the need to consider early screening for other conditions.

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TABLES

Table 1. Baseline characteristics of AAV patients and general population controls.

	AAV patients	General population controls
Number of participants, n	543	2,672
Male sex, n (%)	291 (53.6)	1434 (53.7)
Median age at index, years (IQR)	58.7 [48.9, 68.0]	58.7 [48.9, 68.0]
Follow-up, years (median; IQR)	5.1 [2.5, 9.4]	5.2 [2.5, 9.5]
AAV type, n (%)		N/A
GPA	316 (58.2)	
MPA	157 (28.9)	
EGPA	68 (12.5)	
Missing	2 (0.4)	
ANCA seropositivity, n (%)		N/A
PR3-ANCA	286 (52.7)	
MPO-ANCA	188 (34.6)	
ANCA negative	65 (12.0)	
Missing	4 (0.7)	

AAV: ANCA-associated vasculitis; GPA: Granulomatosis with Polyangiitis; MPA: Microscopic Polyangiitis; EGPA: Eosinophilic Granulomatosis with Polyangiitis; ANCA: Anti-Neutrophil Cytoplasmic-Antibody, PR3: Proteinase 3; MPO: Myeloperoxidase; NA: Not applicable.

Table 2. Comparison of incident morbidities between AAV patients and general population controls during follow-up. Abbreviations: AAV – ANCA-associated vasculitis. *A full list of conditions encompassed by this term is provided in the **Appendix**.

	AAV patients, n (%)	General population controls, n (%)	p-value
Cardiac arrhythmias	49 (9.6)	119 (5.0)	<0.0001
Cardiovascular disease	61 (12.6)	236 (9.5)	0.042
Chronic pulmonary disease	46 (9.7)	120 (4.7)	<0.0001
Depression	<5 (<0.9)	21 (0.8)	0.749
Diabetes mellitus	37 (7.2)	94 (3.6)	<0.0001
Dementia	6 (1.1)	32 (1.2)	0.846
Hypertension	92 (19.7)	234 (9.4)	<0.0001
Hypothyroidism	21 (4.0)	34 (1.3)	<0.0001
Osteoporosis	29 (5.4)	22 (0.8)	<0.0001
Peptic ulcer disease	<5 (<0.9)	21 (0.8)	0.918
Pulmonary circulation disorders*	31 (5.8)	30 (1.1)	<0.0001
Valvular disease	46 (8.7)	80 (3.0)	<0.0001

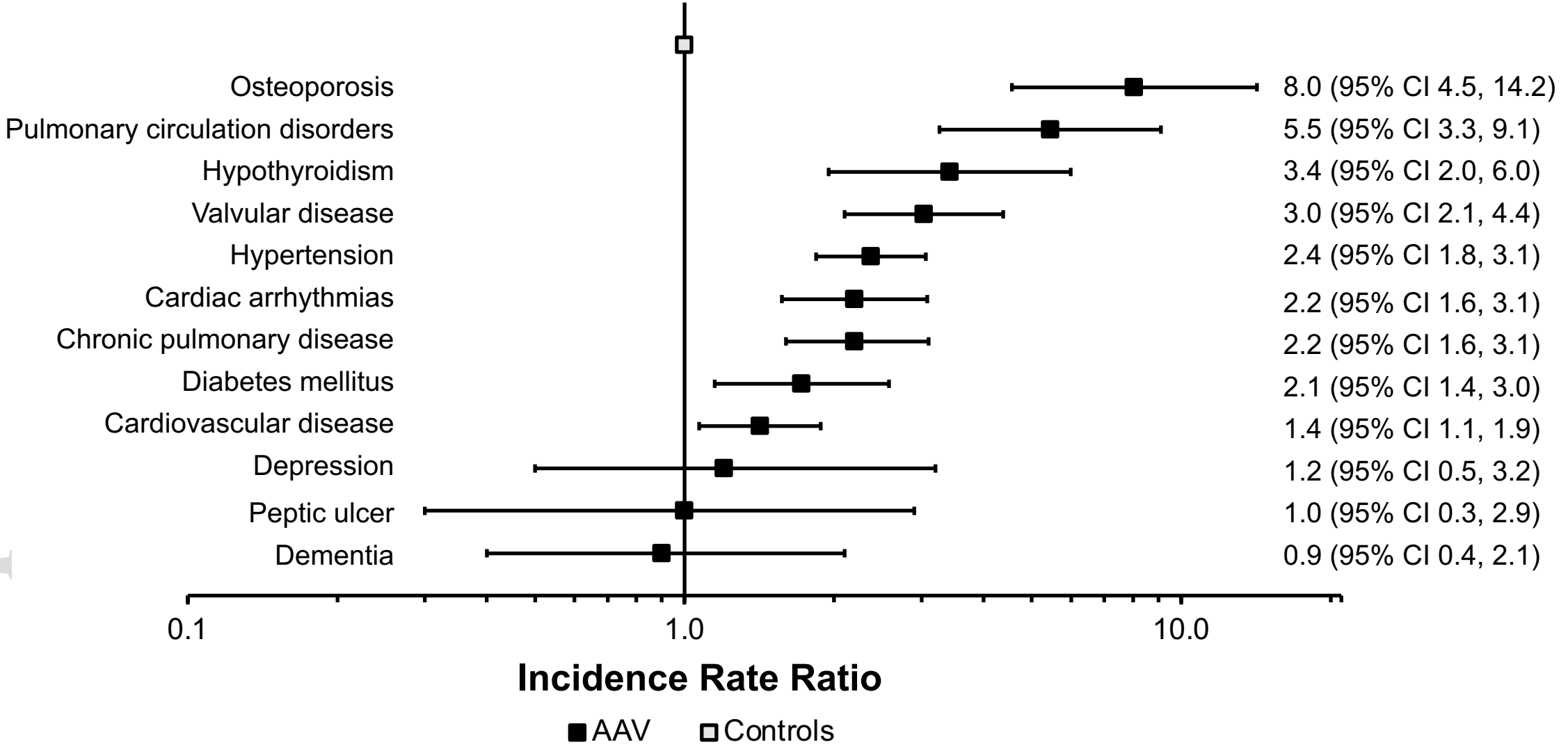
FIGURE LEGENDS

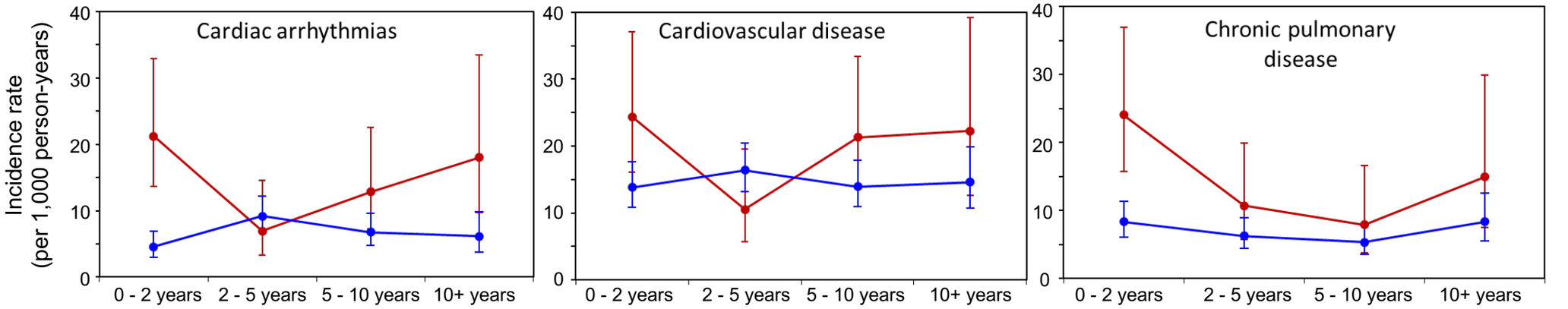
Figure 1. Comparison of the incidence of individual morbidities in AAV patients with general population controls shown as incidence rate ratios (IRRs). IRRs were adjusted for age, sex, and local health board. The rate of incident morbidity in the general population controls was set as the reference. AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; 95% CI: 95% confidence interval.

Figure 2. Temporal trends in the incidence of individual morbidities in AAV patients (red) and general population controls (blue). AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis. Scale of y-axis is different for hypertension.

Figure 3. Prevalence of morbidities at baseline and cumulative incidence of morbidities and multimorbidity at 1, 2, 5 and 10 years in AAV patients and general population controls. AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis. P for χ^2 test for trend <0.0001 for all timepoints. AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis.

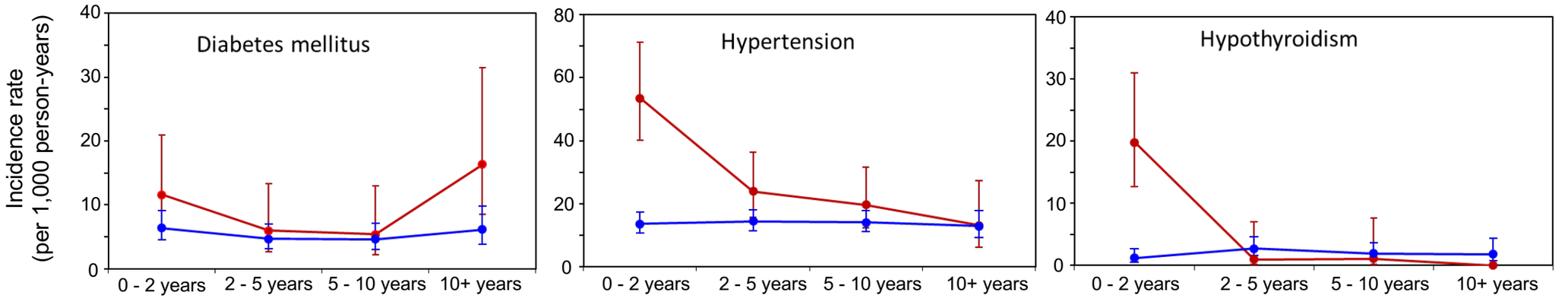
Figure 4. Alluvial plot illustrating the relationship between number of incident morbidities and total excess healthcare expenditure during study follow-up in AAV patients (n=502). AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis.





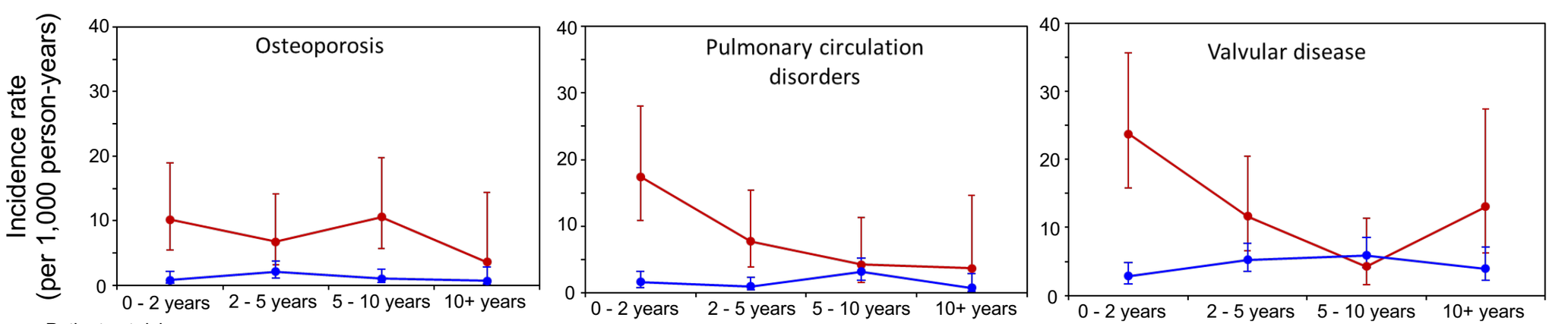
Patients at risk

AAV	510	421	263	117	487	401	248	112	474	249	249	110
General population	2591	2146	1341	567	2487	2070	1295	575	2577	2130	1334	584



Patients at risk

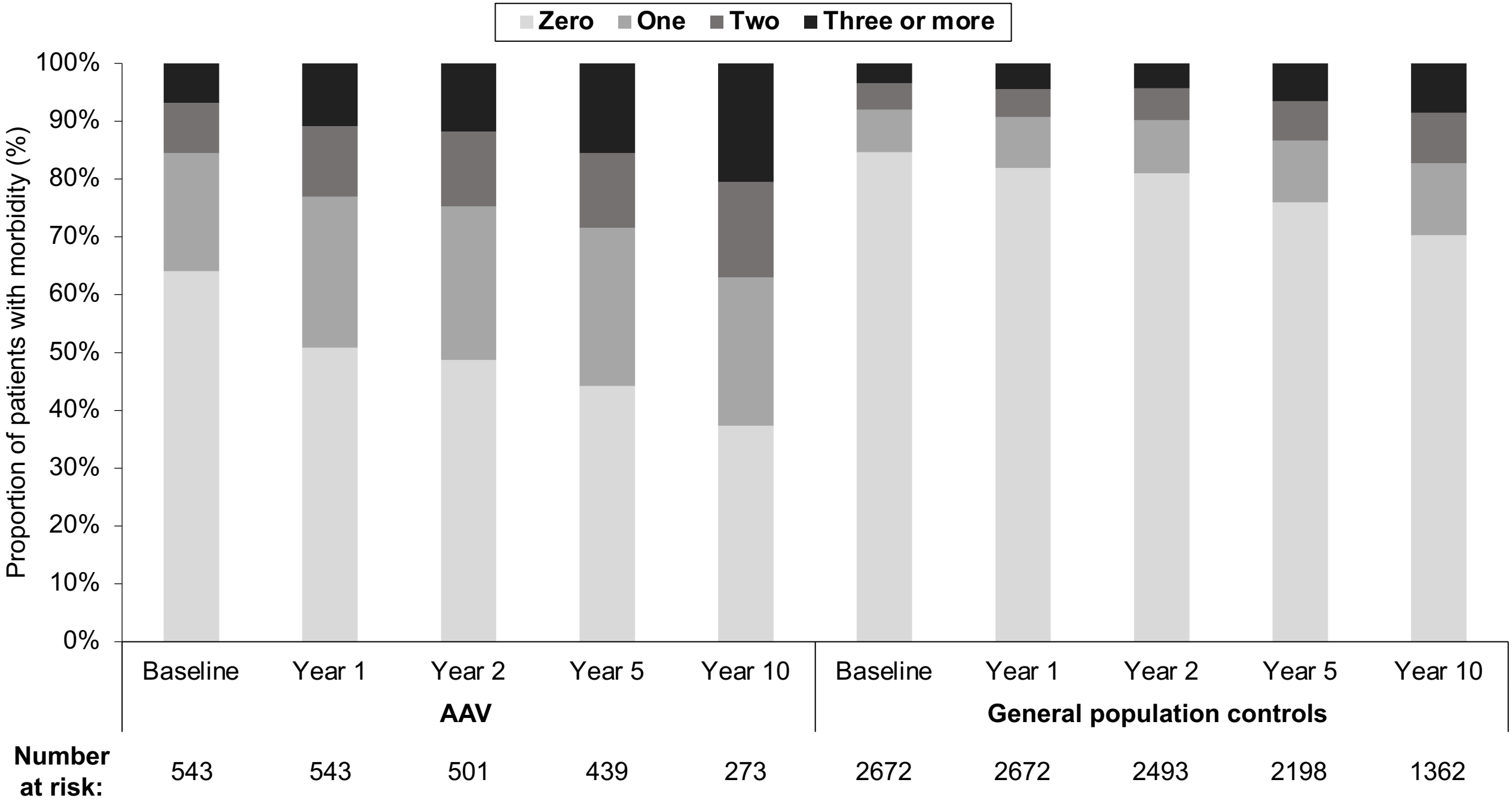
AAV	515	419	263	114	466	383	242	112	521	425	266	116
General population	2604	2152	1346	587	2492	2071	1305	581	2635	2168	1247	588

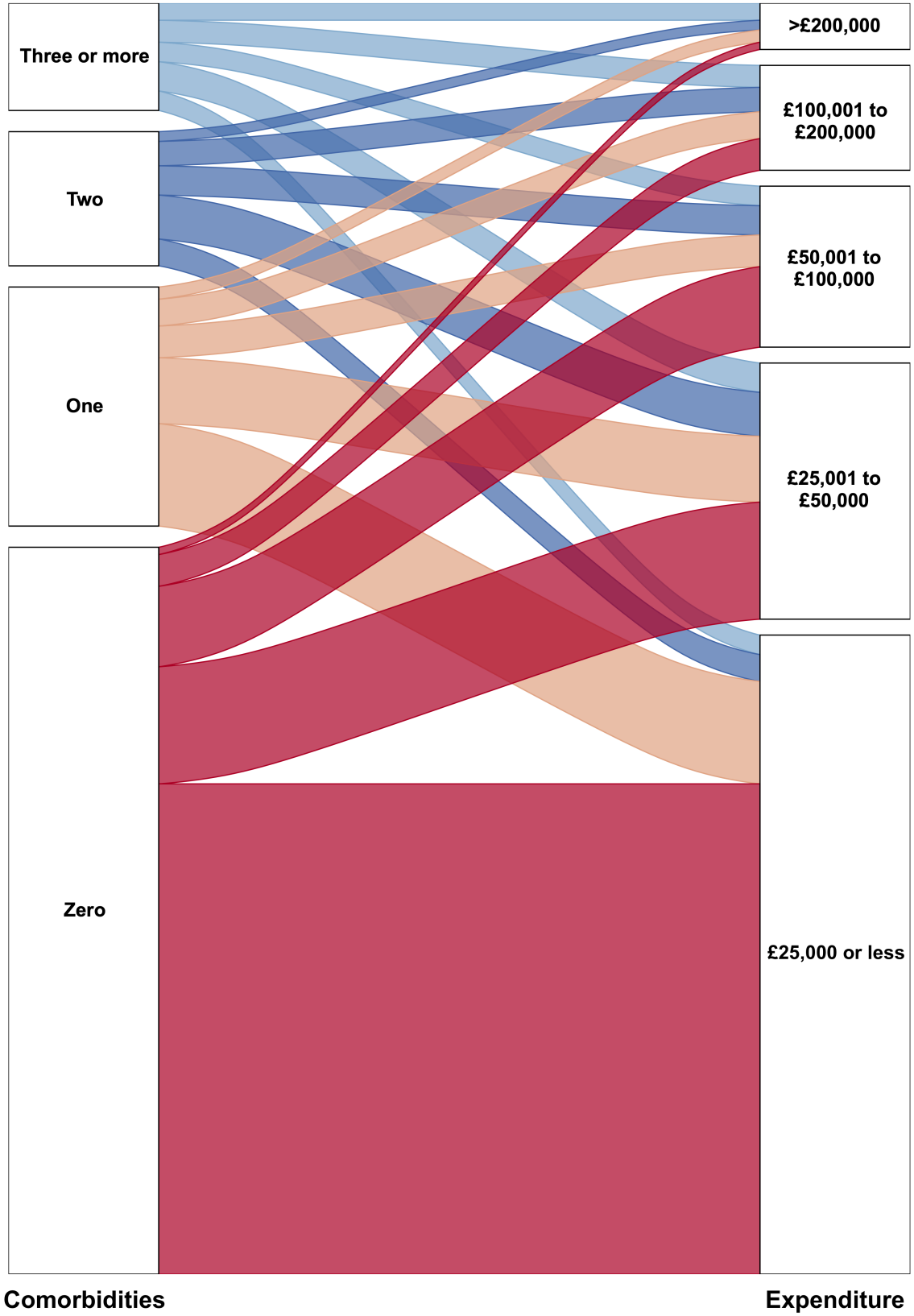


Patients at risk

AAV	536	434	269	117	532	433	270	116	527	431	269	115
General population	2659	2191	1360	590	2658	2188	1359	589	2631	2172	1351	588

AAV **General population**


Zero
One
Two
Three or more
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion of patients with morbidity (%)
Baseline
Year 1
Year 2
Year 5
Year 10
Baseline
Year 1
Year 2
Year 5
Year 10
AAV
General population controls
Number at risk:
543
543
501
439
273
2672
2672
2493
2198
1362



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